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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,882	03/11/2002	Richard William Titball	41577/270459	2737

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EXAMINER	
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ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/070,882	TITBALL ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,23,26-31 and 33-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 23, 26-31 and 33-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 10/29/07 in response to the non-final Office Action mailed 05/02/07.

Status of Claims

2) Claims 1, 23, 26 and 31 have been amended via the amendment filed 10/29/07.

Claims 25 and 32 have been canceled via the amendment filed 10/29/07.

Claims 33-35 have been added via the amendment filed 10/29/07.

Claims 1, 23, 26-31 and 33-35 are pending and are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Moot

5) The rejection of claims 25 and 32 made in paragraph 16 of the Office Action mailed 05/02/07 under 35 U.S.C § 112, first paragraph, as containing new matter, is moot in light of Applicants' cancellation of the claims.

6) The rejection of claims 25 and 32 made in paragraph 17 of the Office Action mailed 05/02/07 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is moot in light of Applicants' cancellation of the claims.

7) The rejection of claims 25 and 32 made in paragraph 18 of the Office Action mailed 05/02/07 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

Rejection(s) Withdrawn

8) The rejection of claims 1, 23 and 26-31 made in paragraph 16 of the Office Action mailed 05/02/07 under 35 U.S.C § 112, first paragraph, as containing new matter, is withdrawn in light of Applicants' amendment to the base claim. A new rejection is set forth below to address the claims as amended.

9) The rejection of claims 1, 23 and 26-31 made in paragraph 17 of the Office Action mailed 05/02/07 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the full scope, is withdrawn in light of Applicants' amendment to the claims and/or the base claim. A new rejection is set forth below to address the claims as amended.

10) The rejection of claims 1, 23 and 26-31 made in paragraph 18 of the Office Action mailed 05/02/07 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims and/or the base claim.

New Rejection(s) Necessitated by Applicants' Amendment

The new rejection(s) set forth below are necessitated by Applicants' amendments to the claims and/or submission of new claims.

Rejection(s) under 35 U.S.C § 112, First Paragraph (New Matter)

11) Claim 1 and the dependent claims 23 and 25-32 are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1, as amended, is drawn to a method of 'causing' expression of a desired 'heterologous' protein 'in mucosal cells' of a mammal, the method comprising placing a nucleotide sequence encoding the 'heterologous' protein under the control of a promoter consisting of a nucleotide sequence of SEQ ID NO: 2, 'the promoter being operatively interconnected to the nucleotide sequence encoding the heterologous protein', in a recombinant gut-colonizing 'bacterium, orally' administering the 'bacterium' to the mammal, and causing expression of the desired heterologous protein in mucosal cells 'of the mammal'. The currently claimed method of 'causing' expression of a desired heterologous

protein 'in mucosal cells' of a mammal includes the steps of: (a) placing a nucleotide sequence encoding the protein to be expressed under the control of a promoter consisting of a nucleotide sequence of SEQ ID NO: 2 in a recombinant gut-colonizing bacterium; (b) 'orally' administering the bacterium to the mammal; and (c) causing expression of the desired heterologous protein in mucosal cells 'of the mammal'. As recited currently, while the administration of the recombinant gut-colonizing bacterium is required to be by oral route, the mucosal cells of the mammal wherein the heterologous protein is expressed can be any mucosal cells, including non-oral and non-GI tract mucosal cells. The limitation 'heterologous protein' encompasses a heterologous protein for example of a non-oral and non-gastrointestinal pathogen, a HIV protein, a eukaryotic protein, a cancer protein etc. and the limitation 'mucosal cells' of a mammal include nasal cells, vaginal cells etc. Applicants state that support for the claim amendments can be found at lines 1-4 of page 1, lines 6-9 of page 5, lines 21-23 of page 8, lines 12-15 of page 16, and lines 24-36 of page 4 of the instant specification. However, the description in these parts of the specification are not supportive of the now claimed method that causes expression of a heterologous protein in any generic or specific mucosal cells of a mammal to which the recited recombinant gut-colonizing bacterium is orally administered. Note furthermore that claim 1 as originally filed neither included oral administration step nor expression of a heterologous protein in generic mucosal cells. The limitation 'in mucosal cells' has no descriptive support. Therefore, the currently claimed method constitutes new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after 608.04(c).

Applicants are invited to point to specific line and page numbers of the specification, as originally filed, that provide descriptive support for the limitations identified above, or alternatively, remove the new matter from the claim. Applicants should specifically point out the support for any amendment made to the disclosure. See MPEP 714.02 and 2163.06.

Rejection(s) under 35 U.S.C § 112, First Paragraph (Scope of Enablement)

12) Claims 1, 23 and 25-32 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a method of inducing a serum or mucosal antibody response against F1 antigen of *Yersinia pestis* in a mammal comprising orally administering to said mammal a dosage of an attenuated recombinant *Salmonella* spp. expressing said F1

antigen wherein said *Salmonella* spp. comprises the nucleotide sequence encoding said F1 antigen under the control of a promoter consisting of the nucleotide sequence of SEQ ID NO: 2, said promoter being operatively interconnected to the nucleotide sequence, does not reasonably provide enablement for a method of enhancing expression of any desired protein in mucosal cells of a mammal, said method comprising placing a nucleotide sequence encoding the protein to be expressed under control of a promoter having the nucleotide sequence of SEQ ID NO: 2 in a generic recombinant gut-colonizing bacterium, orally administering the bacterium to the mammal, and causing expression of the desired heterologous protein in mucosal cells, as claimed broadly. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to reproducibly make and use the full scope of the invention as claimed.

Instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

Claim 1, as amended, is drawn to a method of causing expression of a desired heterologous protein 'in mucosal cells' of a mammal, the method comprising placing a nucleotide sequence encoding the heterologous protein under the control of a promoter consisting of a nucleotide sequence of SEQ ID NO: 2, the promoter being operatively interconnected to the nucleotide sequence encoding the heterologous protein, in a recombinant gut-colonizing bacterium, orally administering the bacterium to the mammal, and causing expression of the desired heterologous protein in mucosal cells of the mammal. Thus, the currently claimed method of causing expression of a desired heterologous protein 'in mucosal cells' of a mammal includes the steps of: (a) placing a nucleotide sequence encoding the protein to be expressed under the control of a promoter consisting of a nucleotide sequence of SEQ ID NO: 2 in any recombinant gut-colonizing bacterium; (b)

'orally' administering the bacterium to the mammal; and (c) causing expression of the desired heterologous protein in any mucosal cells of the mammal. As recited currently, while the administration of the recombinant gut-colonizing bacterium is required to be by oral route, the mucosal cells of the mammal wherein the heterologous protein is expressed can be any mucosal cells, including non-oral and non-GI tract mucosal cells. The generic limitation 'mucosal cells of a mammal' encompasses intranasal cells, vaginal cells and other non-oral and non-gastrointestinal mucosal cells. The limitation 'heterologous protein' encompasses a heterologous protein for example of a non-oral and non-gastrointestinal pathogen, a HIV protein, Ebola viral protein, prion protein, a eukaryotic protein, a cancer protein etc. The method of claims 23, 26-28 and 31 is required to induce 'a protective immune response' against a generically recited 'pathogen' upon *oral* administration of the recombinant gut-colonizing bacterium expressing the heterologous protein in any mucosal cells of the mammal, including non-gastrointestinal mucosal cells. The limitation 'pathogen' encompasses an oral pathogen, a gastrointestinal pathogen, a non-oral pathogen, a non-gastrointestinal pathogen, a respiratory pathogen, a urogenital pathogen, a cerebral pathogen, prion, viral, bacterial, or parasitic pathogen, intracellular pathogen, anaerobic pathogen etc. The limitation 'gut-colonizing bacterium' encompasses gut-colonizing pathogenic and non-pathogenic bacteria, including aerobic and anaerobic bacteria, and gut-colonizing pathogenic and non-pathogenic bacteria. The limitation 'gut-colonizing bacterium' encompasses highly virulent or invasive bacteria having the ability to cause fatal infections in a mammal upon oral administration. The gut-colonizing pathogenic and non-pathogenic bacteria include various species of *Salmonella*, *Shigella*, *Vibrio*, *Escherichia*, *Lactobacillus*, *Lactococcus*, *Bifidobacterium*, *Bacteroides*, *Clostridium*, *Fusobacterium*, *Peptostreptococcus*, *Ruminococcus*, *Eubacterium*, *Peptococcus*, *Streptococcus agalactiae* etc. The limitation 'gut-colonizing bacterium' in the amended claim 1 is not required to be attenuated, but can be infectious or virulent. However, the last paragraph of page 6 of the specification emphasizes the importance of 'suitably attenuating' recombinant gut-colonizing microorganisms of the instant invention 'so that the host does not experience significant harmful effects as a result of infection by the microorganism', indicating the necessity or requirement for the recited gut-colonizing bacterium to be --attenuated--. Furthermore, the only heterologous protein species that is expressed in an attenuated recombinant *S.*

typhimurium or attenuated *S. typhi* gut-colonizing bacterium species is the F1 antigen of *Y. pestis* under the control of a promoter consisting of the nucleotide sequence of SEQ ID NO: 2. There is no predictability that this can be extended to the expression in mucosal cells of a plethora of heterologous proteins of eukaryotic and prokaryotic origin, or heterologous proteins of innumerable pathogens, including those the site of infection of which excludes the oral or the gastrointestinal tract. For example, if one produced a recombinant *S. typhi* pathogen expressing an encephalitis viral protein and orally administered the same to a mammal, there is no predictability that the protein would be expressed in non-gastrointestinal mucosal cells and induce a protective immune response against the encephalitis virus. The method as broadly claimed includes orally administering to a mammal a non-attenuated gut-colonizing bacterium expressing a heterologous protein of any pathogen to cause expression of the heterologous protein in any mucosal cells of the mammal and/or induction of a protective immune response against the pathogen, which method is not enabled. The enabling disclosure in the instant specification however is limited to a method of inducing a serum or mucosal antibody response against F1 antigen of *Yersinia pestis* in a mammal comprising orally administering to said mammal a dosage of an attenuated recombinant *Salmonella* spp. expressing said F1 antigen wherein said *Salmonella* spp. comprises the nucleotide sequence encoding said F1 antigen under the control of a promoter consisting of the nucleotide sequence of SEQ ID NO: 2, said promoter being operatively interconnected to the nucleotide sequence. However, beyond this scope, the specification is not enabling for a method of causing expression of a representative number of heterologous desired protein species including those from pathogens in a representative number of mucosal cells of a human or non-human mammal, said method comprising placing a nucleotide sequence encoding the protein to be expressed under control of a promoter consisting of a nucleotide sequence of SEQ ID NO: 2 in a generic recombinant gut-colonizing bacterium, orally administering the bacterium to the mammal, and causing expression of the desired protein in said mucosal cells and/or inducing a protective immune response against the pathogen, as claimed broadly. A considerable amount of undue experimentation would have been required by one of ordinary skill in the art at the time of the effective filing date of the instant application to reproducibly practice the invention as claimed, due to the lack of specific guidance and direction, the lack of disclosure enabling the full scope, the

unpredictability of inducing a protective immune response against any pathogen by oral administration of a recombinant gut-colonizing bacterium expressing any heterologous protein in any mucosal cells of the mammal, the breadth of the claims, and the quantity of experimentation necessary. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first paragraph.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

13) Claims 1, 26-31 and 33-35 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 1, as amended, is indefinite, confusing, and appears to lack proper antecedent basis in the limitation 'mucosal cells of the mammal' (see last two lines). Line 2 of the claim already includes the limitation: 'mucosal cells' of a mammal. Does it mean that the 'mucosal cells' recited at the end of the claim are different from the 'mucosal cells' recited in line 2 of the claim? If not, it is suggested that Applicants provide proper antecedent basis by replacing the above-identified limitation with the limitation --the mucosal cells of the mammal--.

(b) Claim 28 is indefinite, incorrect, and has improper antecedent basis in the limitation: 'the recombinant gut-colonising microorganism'. Claim 28 depends from the amended claim 1, which does not include the limitation of any recombinant gut-colonising 'microorganism'.

(c) Claim 33 is indefinite in the limitation: 'method of inducing a serum or mucosal antibody response', because it is unclear in whom said antibody response is being induced.

(d) Claim 33 is vague and indefinite in the limitation: 'an F1-antigen of *Yersinia pestis*' (see line 2). Does it mean than *Yersinia pestis* produces more than one F1-antigen, one of which is expressed in the recited attenuated *Salmonella* spp.? If not, it is suggested that Applicants delete the limitation 'an'.

(e) For the purpose of distinctly claiming the subject matter, it is suggested that Applicants replace the limitation 'a nucleotide sequence' with the limitation --the nucleotide sequence-- in line 4 of the claim.

(f) Claims 23 and 26-31, which depend from claim 1, and claims 34 and 35, which depend from claim 33, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Remarks

14) Claims 1, 23, 26-31 and 33-35 stand rejected.

15) Applicants' amendments necessitated the new ground(s) of rejection presented in this Office action. THIS ACTION IS MADE FINAL. Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

16) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. The Fax number for submission of amendments, responses and/or papers is (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

17) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

18) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854.

A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Shanon Foley, can be reached on (571) 272-0898.

January, 2008

S. DEVI, PH.D.
PRIMARY EXAMINER